DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region d18416

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 331-2906

March 23, 1998

RELEASE

REVIEWED BY C.O. WM 3/24/98 DATE

WARNING LETTER

Raymond Sackler, M.D.
President
PF Laboratories, Inc.
700 Union Boulevard
Totowa, NJ 07512

File No.: 98-NWJ-18

Dear Dr. Sackler:

During an inspection of your manufacturing facility located at 700 Union Blvd., Totowa, NJ from February 4, 1998 through February 23, 1998, An Investigator from this office documented deviations from Current Good manufacturing Practice Regulations (cGMP'S), Title 21, Code of Federal Regulations (CFR), Parts 210 & 211. These deviations were noted on the Form FDA-483, List of Inspectional Observations, issued to you at the close of the inspection.

The above stated inspection revealed that drug products manufactured at your facility are considered to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the ACT), in that the methods used in, or the facilities and/or controls used in the manufacturing are not in conformance with cGMP's as follows:

1) Deviations occurring during the processing of batches which may have been attributable to equipment problems or calculation errors, were not detected by your Quality Unit until out of specification test results were observed. These deviations necessitated the reworking of the following batches:

   A) Dihydrocodeine Plus Capsules Lot 9KJ failed in process blend sampling for Dihydrocodeine Bitartrate assay with a result of 12.27 mg [redacted] An additional 20 minute mixing step was performed to the final blend.

B) Water was added to Morphine Sulfate Immediate Release Liquid Lot E70 (10 mg/5 ml, Exp. 9/00) and Lot E68 (20 mg/5 ml, Exp. 10/00) to compensate for out of specification assay results of 12.06 mg/5 ml and 24.6 mg/5 ml, respectively [redacted]

C) Water was added to Senokot Syrup lot H850 and Senokot Pediatric Syrup lot H870 to compensate for out of specification assay results of 2.6 mg/ml and 2.8 mg/ml, respectively [redacted]

In addition, there were no established protocols in place to address the above product reworks.

2) Your firm failed to assure that all steps used in the manufacture of pharmaceutical products were documented in associated batch records. In each case, your quality unit approved the batch records and subsequently released the products. For example:

A) An additional 20 minute mixing step was implemented during the manufacture of Dihydrocodeine Plus Capsules, Lot 8EY, due to an out of specification blend assay result. This additional manufacturing step was not documented.

B) Additional water added to Morphine Sulfate Immediate Release Liquid Lot E70 (10 mg/5 ml) and lot E68 (20 mg/5 ml) due to out of specification assay results was not documented.

C) Additional water added to Senokot Syrup, Lot H850 and Senokot Pediatric Syrup, Lot H870 due to out of specification assay results was not documented.

3) Laboratory investigations conducted by your firm were inadequate. For example:

A) An initial out of specification assay result (14.2 mg) for Dihydrocodeine Plus Capsules, Lot 8EY, was obtained using a radial compression method which was approved in the original ANDA for use by the original holder of the ANDA. The radial compression method was not evaluated for use in your laboratory. In

addition, the out of specification result was invalidated using an experimental HPLC method.

B) An investigation was not performed to determine the identity or cause of black spots on core tablets found during the validation run of MS Contin 200 mg tablets, lot 3GM.

The above list is not intended to be all-inclusive of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deficiencies. Failure to implement corrective measures may result in regulatory action, including seizure and/or injunction, without further notice.

We are in receipt of your written response, dated March 3, 1998, to the FDA-483 List of Inspectional Observations. We offer the following comments and request additional information as they correspond to the FDA-483 observations:

Your response to observation #1 stated that the out of specification blend assay result was due to a lack of granulation uniformity. As a result, you blended all ingredients for an additional 20 minutes. Initiating a reprocessing step that is not validated and not included in a ANDA/NDA is unacceptable (this statement also pertains to FDA observations #3 & 4). Your response further states (in response #2) that you will validate the additional blend time for three batches. Once this is completed, which manufacturing process will be used: The originally validated and approved process in which the ingredients are blended for 20 minutes, or the new process where you blend all of the ingredients for [redacted] Has lot 9KJ been implemented into your firm's stability monitoring program? Will you supplement your application in lieu of your proposed changes in the manufacturing process?

Your firm's response #2 states that one method for the testing of all Dihydrocodone Plus Capsules will be used for future process validation studies. Which method is your response referring to? Will this method also be used to release finished product? How many lots were released with the radial compression method? Did the crossover study specified in your response compare the approved radial

compression method and the HPLC method? Has the HPLC method been validated?

Your firm's response #3 & 4 stated that although the isolated batch adjustments involving the addition of water were not validated, dissolution of the active ingredient in water was previously validated. Although the initial addition of water was validated, supplementary water additions were not. The rationale for deviating from established batch records must be supported by data (development and/or validation data) prior to implementation. Your responses also stated that all effected lots were tested against established specifications after (water) adjustment. Was this testing limited to finished product testing?

Your firm's response #6 states that the quality standard for Senokot tablets has been revised to indicate the method to be used for release. Please supply a copy of the quality standard and the method to be used with your response.

Regarding your firm's response #8, please supply copies of the revised procedures.

You should notify this office in writing, within 15 working days of receipt of this letter, of the additional steps you have taken to correct the noted deficiencies. If corrective action cannot be completed within 15 working days, state the reason for the delay and the timeframe within which corrections will be completed.

Your response should be sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Boulevard, 3rd Floor, Parsippany, NJ 07054. Attention: William Mestrandrea, Acting Compliance Officer.

Very truly yours,

Edward-H. Welkens, Jr

DOUGLAS ELLSWORTH
District Director
New Jersey District Office

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

WM:slm